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Do Variations in Mast Cell Hyperplasia Account for Differences in Radiation-Induced Lung Injury among Different Mouse Strains, Rats and Nonhuman Primates?

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Abstract

The role of mast cell infiltrates in the pathology of radiation damage to the lung has been a subject of continuing investigation over the past four decades. This has been accompanied by a number of proposals as to how mast cells and the secretory products thereof participate in the generation of acute inflammation (pneumonitis) and the chronic process of collagen deposition (fibrosis). An additional pathophysiology examines the possible connection between mast cell hyperplasia and pulmonary hypertension through the release of vasoactive mediators. The timing and magnitude of pneumonitis and fibrosis are known to vary tremendously among different genetic mouse strains and animal species. Therefore, we have systematically compared mast cell numbers in lung sections from nine mouse strains, two rat strains and nonhuman primates (NHP) after whole thorax irradiation (WTI) at doses ranging from 10–15 Gy and at the time of entering respiratory distress. Mice of the BALB/c strain had a dramatic increase in interstitial mast cell numbers, similar to WAG/Rij and August rats, while relatively low levels of mast cell infiltrate were observed in other mouse strains (CBA, C3H, B6, C57L, WHT and TO mice). Enumeration of mast cell number in five NHPs (rhesus macaque), exhibiting severe pneumonitis at 17 weeks after 10 Gy WTI, also indicated a low response shared by the majority of mouse strains. There appeared to be no relationship between the mast cell response and the strain-dependent susceptibility towards pneumonitis or fibrosis. Further investigations are required to explore the possible participation of mast cells in mediating specific vascular responses and whether a genetically diverse mast cell response occurs in humans.

INTRODUCTION

The human lung is among the most radiosensitive tissues of the body; it presents as a delayed but acute onset of an inflammatory pneumonitis reaction at 2 to 6 months after radiation exposure that may or may not progress to chronic pulmonary fibrosis (1). Radiation pneumonitis is a particularly severe and life-threatening condition when large lung volumes are exposed in radiotherapy (2–4) or accidental nuclear events (5, 6). The long latency before onset of injury is consistent with initial DNA damage to slow proliferating

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epithelial and/or endothelial cells that then rapidly evolves into a sterile inflammatory process involving a complex interplay of various inflammatory cell infiltrates and cytokines (7, 8). Among the possible cell types actively recruited in radiation lung pathology, mast cells are of interest because they have multifunctional properties that initiate not only IgE-dependent allergic diseases but also play a fundamental role in innate and adaptive immune responses and inflammatory autoimmune diseases (9). An influx of mast cells have been documented as an accompaniment to radiation pneumonitis (alveolitis), most commonly in experimental studies in rats, where their pathophysiological significance has been a subject of continuing investigation over the past four decades (10–18). The timing and extent of pneumonitis and fibrosis are known to vary tremendously among heterogeneous mouse strains and animal species (19–23). We systemically compared pulmonary mast cell numbers during the period of lethal lung injury in various rodent strains and in rhesus macaques to determine if the level of mast cell hyperplasia is diverse and if it associates with genetically determined variations in pneumonitic or fibrogenic responses.

MATERIALS AND METHODS

Male BALB/c (BALB/cAnNCrl, Charles River Laboratories International, Inc., Wilmington, MA), and CBA/J, C57BL/6J, C57L/J, C57BR/cdJ and A/J mice (Jackson Laboratory, Bar Harbor, ME) were housed under identical conditions in approved facilities at the Massachusetts Institute of Technology (MIT). Male WHT mice (Gray Laboratory, Northwood, Middlesex, UK), male TO mice (Tizzers' Original, Hammersmith Hospital, London, UK) and male August rats (MRC National Institute for Medical Research, Mill Hill, Middlesex, UK) were housed at the Institute of Cancer Research (ICR), Sutton, Surrey, UK. Female and male WAG/RijCmcr rats were housed in a moderate security barrier facility at the Medical College of Wisconsin (MCW). All facilities were free of known pathogenic organisms and experiments were approved by Institutional Animal Care and Use Committees (at MIT and MCW) or performed in accordance with the Protection of Animals Act, United Kingdom (at ICR).

Rhesus macaques were juvenile males of Chinese origin (3–5 kg) obtained from a commercial vendor (AlphaGenesis, Yemassee, SC). Animals were prescreened by tuberculin testing and CT scans of the chest. Animals were socially housed in pairs. All animal procedures were performed in accordance with the Guide for Care and Use of Laboratory Animals and followed protocols for avoidance of pain and discomfort, environmental enrichment and psychological well being approved by the Wake Forest School of Medicine (WFSM) Institutional Animal Care and Use Committee. Wake Forest School of Medicine is accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care.

The different WTI treatments and animals used for comparison of mast cell numbers in the irradiated lungs together with the main pathologies presented at the time of euthanization are shown in Table 1 and as detailed in previous reports for rodents (12, 18, 19, 23, 24). Rhesus macaques were anesthetized with ketamine and dexmedetomidine and placed supine with arms extended overhead and lightly restrained to prevent movement. A single-fraction dose of 10 Gy was delivered to the midline (nominal depth 4.5 cm), using 6 MV X rays from a clinical linear accelerator (Varian Medical Systems, Palo Alto, CA). This dose was delivered using isocentric setup for a pair of equally weighted (50% of the dose each) parallel-opposed anterior and posterior beams, 10×12.5 cm^2, at a nominal dose rate of 200 cGy/min. For the anterior beam a 1-cm flexible slab of tissue-equivalent material was placed on the anterior chest to ensure dose build-up to the anterior lung surface, and a 15° physical wedge was placed in the beam, toe-inferiorly, to compensate for the superior-inferior slope of the NHP chest and provide better dose homogeneity to the mediastinum.

The physical condition of the animals were closely monitored and the animals were euthanized during the period of respiratory distress as previously reported (22, 23, 25). NHPs were euthanized 4 months postirradiation. Post-mortem, the rodents' lungs were inflated with 10% neutral buffered formalin and for NHPs, ~1 g samples were immersion fixed in 10% neutral buffered formalin. Tissues were processed for histology and mast cells were selectively stained heterochromatically with azure A (pH 1.5–1.7) or toluidine blue (pH 2–4.6) and counted with a calibrated graticule to assess their numbers per mm^2 lung section.

RESULTS

The radiation doses applied in these studies proved to be lethal. The mast cells were enumerated from animals exhibiting signs of respiratory distress, but at times that varied depending on the strain and species. For most mouse strains (CBA, C57L, C57BR, BALB/c, A/J, WHT and TO) this occurred over 10 to 26 weeks after 10–15 Gy WTI while C57BL/6 mice survived longer to 28–32 weeks after 15 Gy. The type of pathology present at autopsy also varied, with CBA and C57L mice showing exclusive signs of severe pneumonitis (reddened and firm lungs with increased tissue mass) while C57BR, BALB/c, A/J, WHT, TO and C57BL/6 mice presented with a mixture of pneumonitis and pleural effusions (22, 23). August and WAG/Rij rats exhibited similar symptoms of pneumonitis and accumulations of pleural fluid at 7 to 8 weeks after 14 or 15 Gy. While the five rhesus macaques receiving 10 Gy WTI showed overt pneumonitis (multifocal to coalescing regions of increased firmness with tan to grey discoloration) with significant increase in lung tissue mass (average 59 g) compared to three unirradiated controls (average 33 g).

In unirradiated control mice (at 18–28 weeks after sham irradiation) very few mast cells were found throughout the lung tissue (average of 4.4 cells/mm^2 of all mouse strains) while lungs from irradiated CBA, C57L, C57BL/6, A/J, C57BR, WHT and TO mice showed an increase in mast cell numbers (0–62 cells/mm^2), mostly confined to the interstitium (Fig. 1). However, the level of this increase differed dramatically for irradiated BALB/c mice, which showed significantly higher numbers of mast cells (91–369 cells/mm^2) even at relatively low-radiation doses (10 and 12.5 Gy) (Fig. 1). A large influx of interstitial mast cells was also observed in both irradiated August and WAG/Rij rats (average 273 and 269 mast cells/mm^2, respectively), the latter being consistent with the values obtained previously by anti-tryptase staining (18). The five rhesus monkeys receiving 10 Gy showed a much lower average mast cell number (average 22 mast cells/mm^2) than BALB/c mice or rats. This level resembled many of the other mouse strains but was not significantly different from lung sections obtained from three unirradiated control monkeys (average 45 mast cells/mm^2).

Compiled in Fig. 2 are the average mast cell densities from each of the eight irradiated mouse strains together with the values obtained from the two rat strains and the rhesus macaques. Also included for comparison is the published data of mast cell numbers from C3H, C57BL/6 (B6), AKR and KK mouse strains at the time of respiratory distress after 18 Gy WTI (16, 17). Thus an overall evaluation among 11 different mouse strains shows a moderate increase in mast cell infiltrates except in BALB/c mice that exhibited about tenfold higher levels. The latter was similar to the August and WAG/Rij rats while the rhesus macaques had mast cell numbers at levels comparable to the other mouse strains.

DISCUSSION

The wide variation in the type, sensitivity and timing of radiation injury to the lung among different mouse strains as well as among other laboratory animal species offers the opportunity to causally link specific responses such as mast cell hyperplasia with clinically

relevant outcomes. This approach has been employed extensively in associating distinct radiobiological phenotypes with certain candidate genes aimed at allowing the recognition of sensitive patients undergoing radiation therapy and identifying targets for therapeutic intervention (26–28). However, some mouse models produce a response that are not reflected in the human phenotype and may therefore render the applicability of genetic analyses invalid. The major problem has been the inclusion of the C57BL/6 mouse strain in many of these genetic studies based on earlier histological studies that they are “fibrosis prone” (20, 21) and often used with the assumption that they succumb to lethality attributed to this particular lesion. Large accumulations of compressive pleural fluid can, however, account for mortality rather than fibrosis at late times after WTI (12, 23). Thus the elongated time of onset required for complete expression of lung injury and the intrusion of unrelated pleural effusions compromises the proper histological evaluation of pulmonary pathology in this strain. This may limit their application in evaluating therapeutics destined for FDA approval under the so-called “animal rule” (21 CFR Parts 314 and 601) (22, 29, 30). In the current study, C57BL/6 mice showed a significant increase in mast cell numbers that were comparable to many other mouse strains including those that exhibit severe pneumonitis at earlier times and without the problem of pleural effusions (CBA and C57L mice). In the previous study of Haston *et al.* (16) comparing C3H and C57BL/6 strains also at the time of respiratory distress but at a higher dose of 18 Gy, the C57BL/6 strain appeared to show a lower mast cell response. As the issue of survival-limiting pleural effusions was not considered as possibly preventing the full development of both lung injury and mast cell hyperplasia, the claimed association with the pneumonitis (alveolitis) phenotype remains questionable. Additionally, we found that the mast cell numbers were similarly low in the C57L mouse strain but that this is more sensitive to both pneumonitis and fibrosis (23, 30). This enables us to strengthen our conclusion that the pneumonitis or fibrosis phenotypes are not strictly genetically linked to the mast cell response.

The BALB/c mouse strain displayed a remarkable increase in mast cell infiltrates amounting to about tenfold higher cell numbers as compared to the other 10 mouse strains. Indeed, this mouse strain stands out as producing mast cell numbers that are comparable to the high levels found in August and WAG/Rij rats and provides an opportunity to more definitively assess other features that may be causally related to excessive mast cell hyperplasia. Of importance in this regard are the potent vasoactive mediators such as histamine and serotonin that are traditionally known to be secreted by mast cells and are known to be also elevated in the irradiated rat lung (15). These in turn may produce secondary neointimal vascular changes that are typically reported on histological examination of the lungs from irradiated rats (18, 31, 32) and may be causally related to the presentation of pulmonary arterial hypertension and right ventricular hypertrophy (31–33).

The release of renin triggers angiotensin formation as the rate-limiting enzyme in the renin-angiotensin system (RAS) cascade and has recently been documented to be produced locally by mast cells (34) but it remains speculative as to how this would play a role in pulmonary pathophysiology. Incidentally, treatment of rats with captopril, that interferes in the renin-angiotensin system cascade downstream of renin as an inhibitor of angiotensin-converting enzyme (ACE) produced by pulmonary endothelial cells, affords significant mitigation of radiation lung injury (35, 36). Captopril is additionally capable of reducing the number of infiltrating mast cells (37). Further studies are therefore warranted to investigate whether the radiation-induced increase in lung mast cell numbers and local renin release set the stage for renin-angiotensin system in radiation injury and provide a new target for therapeutic intervention. Other treatments known to decrease and/or delay both radiation lung injury and mast cell numbers include anti-CD40 ligand antibody in C57BL/6 (38) and the tyrosine inhibitor imatinib in C3H, AKR and KK mice (17). These agents are pleotropic and known to affect various cell types, thus this correlation does not establish whether a reduction in

mast cell numbers is an effect or cause of the disease. Furthermore, these investigations were limited to mouse strains that exhibit a relatively moderate elevation in mast cell numbers after WTI (Fig. 2) and where there would be an interest to include high mast cell responders such as BALB/c mice.

Our enumeration of mast cells in the lungs of NHPs is of particular relevance to assessing how the mast cell response can be extrapolated to humans experiencing radiation lung injury. In this case, rhesus macaques exhibited severe and potentially lethal radiation pneumonitis at the upper threshold of 10 Gy and at 4 months after WTI; this is entirely consistent with the picture in patients receiving wide-field radiotherapy (3, 4, 30). The mast cell counts, however, were not significantly increased among the five treated monkeys compared to three control animals and clearly contrasted with the high levels observed after irradiation in rats and in the BALB/c mouse strain. A lack of an overt mast cell response was similarly reported in baboons showing radiation lung damage (39). This evidence implies that most primates may not usually be predisposed to the large mast cell infiltrates as witnessed in rats and BALB/c mice. Nonetheless, these comparisons do not exclude the possibility that a certain subpopulation of patients may be identified as being susceptible to mast cell hyperplasia during radiation injury and could benefit from interventional therapies aimed at ameliorating its pathological consequences.

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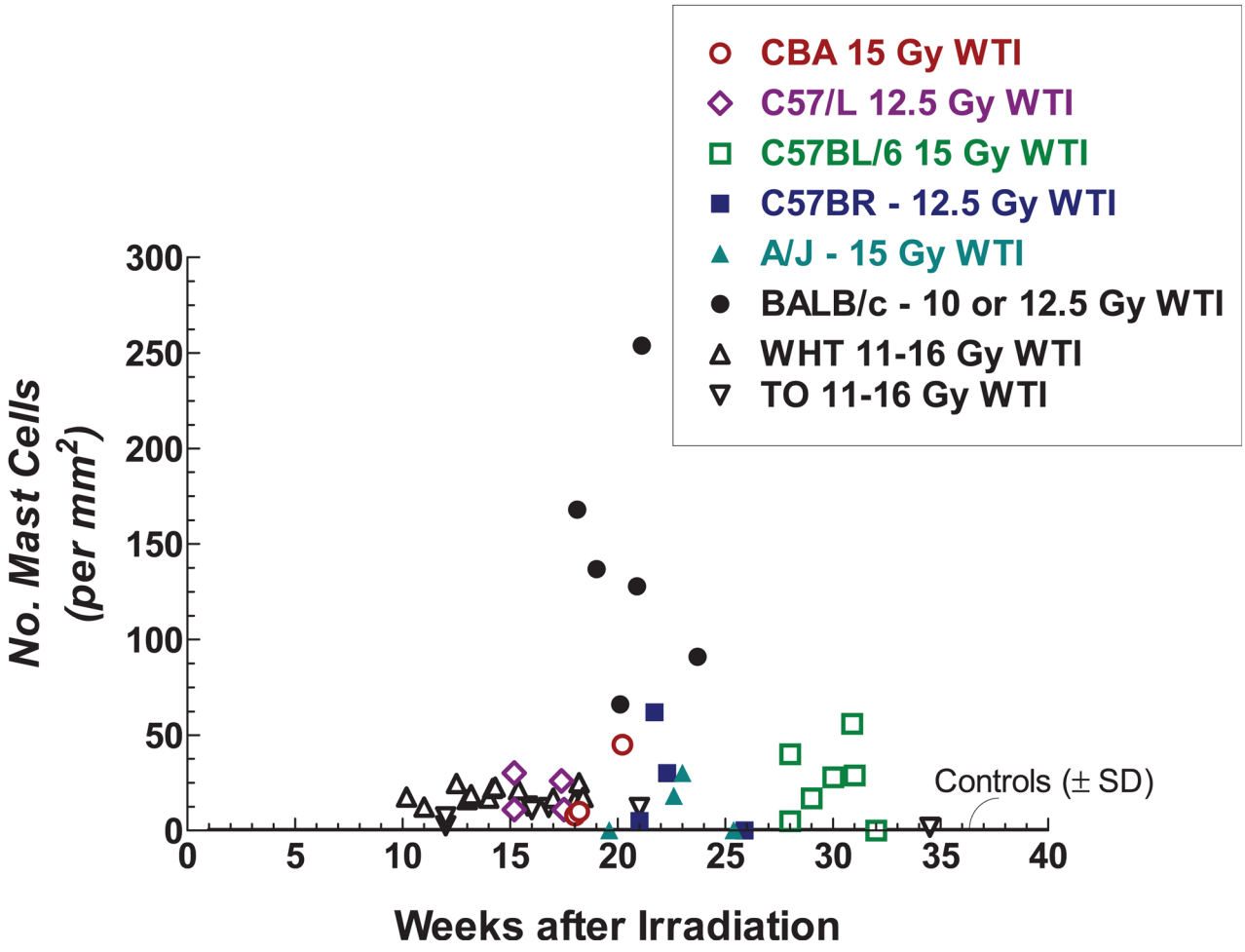

FIG. 1.

Mast cell counts in the lungs from individual mice at the time of respiratory distress after WTI compared and the standard deviation (SD) from unirradiated control mice of all strains. Mast cells in irradiated BALB/c mice were significantly higher than any of the other mouse strains ($P > 0.05$, Mann-Whitney U test).

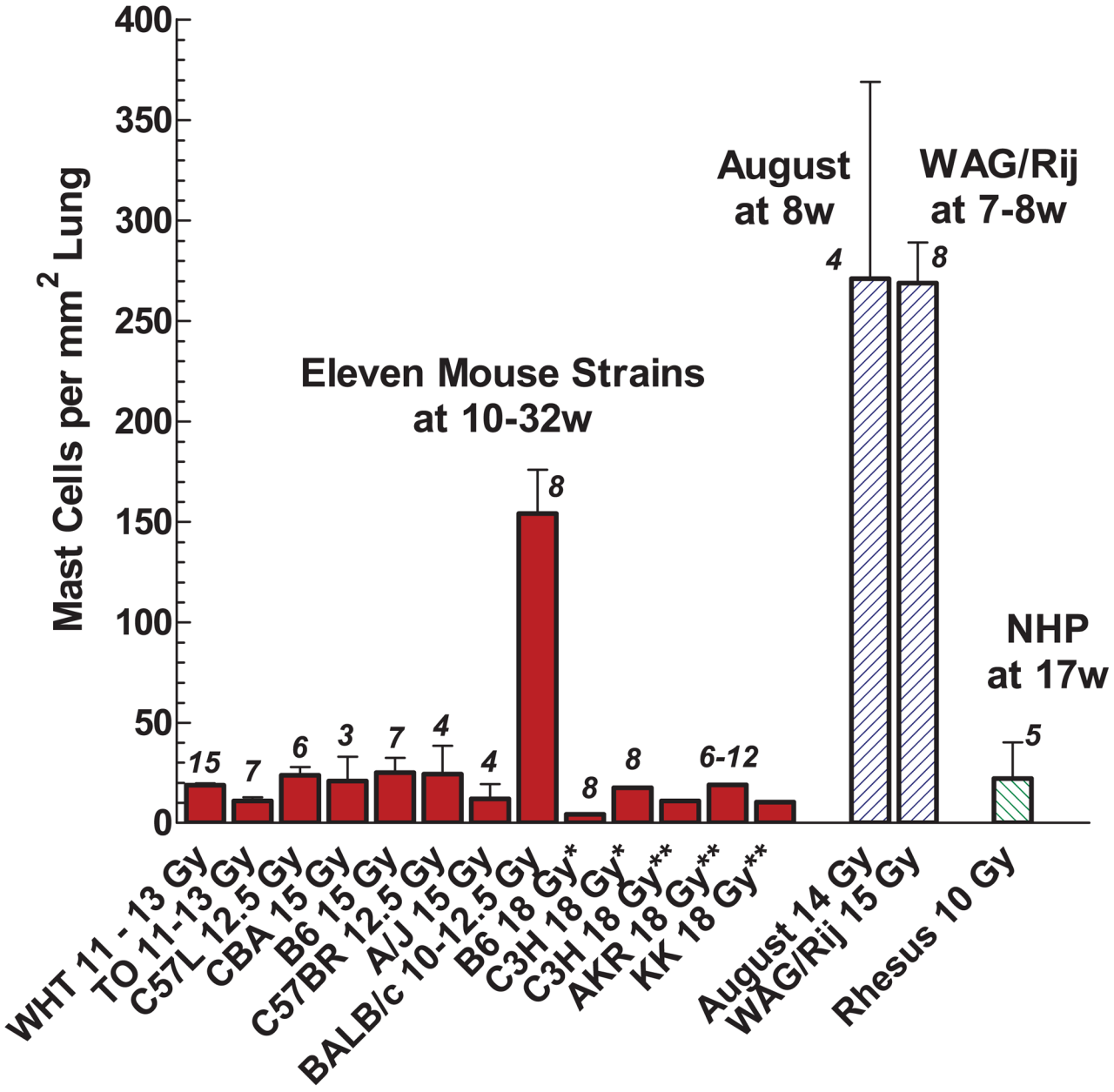

FIG. 2.

Comparison of mean mast cell counts (± 1 SEM) from the irradiated lungs of the different mouse and rat strains and NHPs. Mast cells were enumerated using toluidine blue staining except for lung sections from WHT and TO mice and for August rats where azure A staining was used. Also included for comparison are the mean mast cell numbers reported for C57BL/6 and C3H mice* (16) and for C3H, AKR and KK mice** (17) after 18 Gy WTI. The number of animals per group are indicated.

TABLE 1

Different Animals and WTI Treatments used for Comparison of Mast Cell Responses in the Lung

Institution	Radiation source	Dose (Gy)	Dose rate (Gy/min)	Animal	Age (weeks)	No.	Latent time (weeks)	Main pathology	Ref.
MIT	^{137}Cs γ rays	15	0.51	C57BL/6J mice	12	7	28–32	variable pneumonitis and pleural effusions	23
	^{137}Cs γ rays	15	0.51	CBA/J mice	12	3	18–20	pneumonitis	23
	^{137}Cs γ rays	12.5	0.51	C57L/J mice	12	6	15–18	pneumonitis	23
	^{137}Cs γ rays	10 and 12.5	0.51	BALB/cAnNCrl mice	12	8	18–24	pneumonitis and pleural effusions	22
	^{137}Cs γ rays	15	0.51	C57BR/cdJ mice	12	4	21–26	pneumonitis and pleural effusions	22
	^{137}Cs γ rays	15	0.51	A/J mice	12	4	20–25	pneumonitis and pleural effusions	22
ICR	230 kVp X rays (HVL = 1.9 mmCu)	11–16	1.6	WHT mice	8	15	10–18	pneumonitis and pleural effusions	12, 19
	230 kVp X rays (HVL = 1.9 mmCu)	11–16	1.6	TO mice	8	7	12–34	pneumonitis and pleural effusions	12, 19
	230 kVp X rays (HVL = 1.9 mmCu)	14	1.6	August/Gf.Cbi rats	25	4	8	pneumonitis and pleural effusions	12
MCW	300 kVp X rays (HVL = 1.4 mmCu)	15	1.6	WAG/Rij/MCW	8–10	8	7–8	pneumonitis with or without pleural effusions	18, 24
WFSM	6 MV X rays	10	2	Rhesus macaques	7–11	5	17	pneumonitis	unpublished

Note. Massachusetts Institute of Technology (MIT), Institute of Cancer Research (ICR), Medical College of Wisconsin (MCW) and Wake Forest School of Medicine (WFSM).